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CLINICAL STUDY

Proliferative diabetic retinopathy in long-term diabetic patients with and without clinical osteoarthritis

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Abstract

Objective **To determine whether some long-term diabetic patients with coexisting clinical osteoarthritis (OA) are less likely to develop diabetic retinopathy (DR) than other diabetic patients and whether there is a relation between the timing of the clinical OA onset and DR.**
Design, setting, and participants **Retrospective case–control study of 85 osteoarthritic patients with 20 years or more diabetes (A/DM) control group and of 85 non-osteoarthritic diabetic patients (NoA/DM) matched for age, race, duration, and type of diabetes. Digital fundus photographs were graded for retinopathy in masked manner.**
Results **Glycosylated hemoglobin, hypertension, and smoking showed no significant difference. Twelve out of 85 patients (12.9%) in A/DM group developed proliferative diabetic retinopathy (PDR) whereas 79/85 (92.9%) NoA/DM patients developed PDR ($P<0.001$). The onset of OA symptoms was known in 80/85 of the A/D patients, including 47 patients with onset before or at the same year as DM and 33 patients with relative onset after the year of DM. All the 10 patients with PDR (10/33) developed OA subsequent to their initiation for diabetic treatment while 0/47 A/DM patients with the onset of osteoarthritic symptoms present before or the same year as their onset of diabetes developed PDR ($P<0.001$).**
Conclusion **Our study suggests that in long-term DM, PDR was significantly associated with the absence of concomitant clinical OA. This observation was highly significant if the onset of the arthritis was the same year or before the onset of the diabetes.**
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Introduction

As diabetes has reached epidemic proportions in the United States and around the world, diabetic retinopathy (DR) remains one of the main causes of adult visual impairment and blindness worldwide.[1–5] Currently, 27 million individuals in the United States have diabetes. Diseases such as diabetes often are viewed in isolation, but some recent information suggests an increasing likelihood of its associations with certain diseases, particularly ones with inflammatory components including but not limited to autoimmune diseases.[6]

Arthritis, one of the most prevalent chronic health problems and the leading cause of disability in the United States,[7] affects about 46 million Americans. The term 'arthritis' describes more than 100 different conditions that not only affect joints, including bones, connective tissue, and synovium, but also affect organ systems, such as the vasculature, lungs, intestines, skin, and nervous system, with varying severity and onset at different ages. Osteoarthritis (OA) comprises 80% of all arthritic cases and affects 21 million Americans and the resultant joint destruction has significant immune-related characteristics and is at least auto-inflammatory.[7]

Most arthritic diseases are characterized by the breakdown of the joint cartilage, and subsequent inflammation of the synovium resulting in the production of cytokines and enzymes that further damage cartilage with associated pain, stiffness, and functional limitations. Most forms of arthritis, especially those with strong chronic degenerative

components, for example, OA, are thought to be auto-inflammatory or even, some speculate may be at least in part of autoimmune origin, and recent data suggest that new vessels invade cartilage in the pathogenesis of OA.[8,9]

Results of the Centers for Disease Control study analyzed combined 2005 and 2007 data from the Behavioral Risk Factor Surveillance System and indicated that arthritis prevalence was 52.0% among adults with diagnosed diabetes and also that they have symptoms of arthritis, typically OA.[10] The size of this 'overlap group' of osteoarthritic diabetic patients had previously not been well defined. The aim of the present study is to evaluate retinopathy, particularly proliferative retinopathy in long-term diabetic patients with OA compared with long-term diabetic patients without OA, and to determine whether the timing of the onset of the arthritic symptoms (relative to the onset of the diabetes) is associated with a difference in incidence of DR, especially neovascularization of the retina (proliferative diabetic retinopathy (PDR)).[10] The term proliferative DR has a particular complex fundus picture, for not only do the larger lesions project into the vitreous and acquire an extra dimension, but they are superimposed in a background of simple DR that may be of any degree of severity.[11]

Research design and methods

Institutional Review Board approval was obtained for this retrospective case–control chart study of all patients seen in a single referral retinal practice over the course of 12½ years. The study was confidentially reported in accordance with the principles expressed in the Declaration of Helsinki. Charts of 5376 consecutive new retina patients seen between January 1996 and August 2008 were screened and the charts of 3871 diabetic patients (72% of the clinic population) were identified. Of these diabetic patients, 85 had both coexisting OA and long-term diabetes mellitus (20 years or more) (A/DM), 55 insulin-dependent, and 30 non-insulin-dependent diabetes mellitus. The diagnosis of diabetes mellitus was established by a previous physician diagnoses and the year of treatment initiation was gathered from the chart record. No specific diabetes-related immunologic testing, for example, testing for autoantibodies for insulin or islet cells, was conducted.

The information about a patient having OA obtained during the first visit at the clinic within the 'Review of Systems'. If patients self diagnosed themselves as having chronic joint pain, a questionnaire based on the American Academy of Rheumatology Arthritis questionnaire was administered by the screening nurse. This questionnaire specifically obtained vital information and history of the onset of first arthritis/joint pain symptoms, morning stiffness and length, characteristic of joint pain, history of joint or back surgery, use of pain medications, results of previous arthritis-related blood testing, and any previous rheumatoid/inflammatory serologic testing. Patients were specifically asked whether they had ever been classified as having a specific rheumatologic diagnosis, such as OA, rheumatoid arthritis, gout, lupus, or other diseases associated with chronic joint pain, such as inflammatory bowel disease.[12] The year of onset of arthritic symptoms in the osteoarthritic group was determined from the medical record. Criteria for 'without arthritis' included denial of any history of clinical arthritis or limitation of activity due to arthritic symptoms or history of joint problems.

The control group patients came from the same retinal office patient base and comprised 85 patients with long-term diabetes but no history of arthritis (NoA/DM). These patients had specifically denied a history of arthritis and/or chronic joint pain and were matched with the A/DM patients 1 : 1 for age, gender, race, duration, and type of diabetes (Table 1). To compile the matching control patients (NoA/DM) a total of 967 office charts were screened. The charts were pulled from the shelves of the file room randomly by the office secretary and the patient characteristics were matched for study criteria by the main investigator who was in charge of the patients.

All selected patient charts were examined for history of hypertension, chronic use of aspirin, use of NSAIDS or other pain medication, percent hemoglobin A1c, and type of referring doctor (general eye care specialist (GECS; such as general ophthalmologist or optometrist), or an internal medicine/family practice doctor (IM/FP).

Study sample size was determined by inclusion of all consecutively seen diabetic patients with 20 or more

Table 1 Patients' characteristics

ATTRIBUTES	A/DM ($n = 85$)	NoA/DM ($n = 85$)	*P*-value
Age, years, mean ± S.D.	68.15 ± 12.27	67.38 ± 10.81	0.25 NS*
DM duration range, yrs	20–54 28.4 ± 5.66	20–56 27.7 ± 5.54	0.55 NS*
IDDM	55	55	0.87 NS**
NIDDM	30	30	0.87 NS**
Gender, female	49	48	1.0 NS**
Race (Caucasian)	84	84	0.48 NS**
Hypertension	61	59	0.86 NS**
Smoking	9	7	0.79 NS**
HbA1c ± S.D.	7.49 ± 0.92	7.55 ± 1.33	0.81 NS*

Abbreviations: NS, non-significant; A/DM, osteoarthritic patient group with long-term diabetes of 20 years or more duration; NoA/DM, long-term diabetic patient without co-existing clinical arthritis; IDDM, insulin dependent diabetes; NIDDM, non-insulin dependent diabetes.
*Student *t*-test, two sided.
**Chi-Square test for standard deviation, two sided.

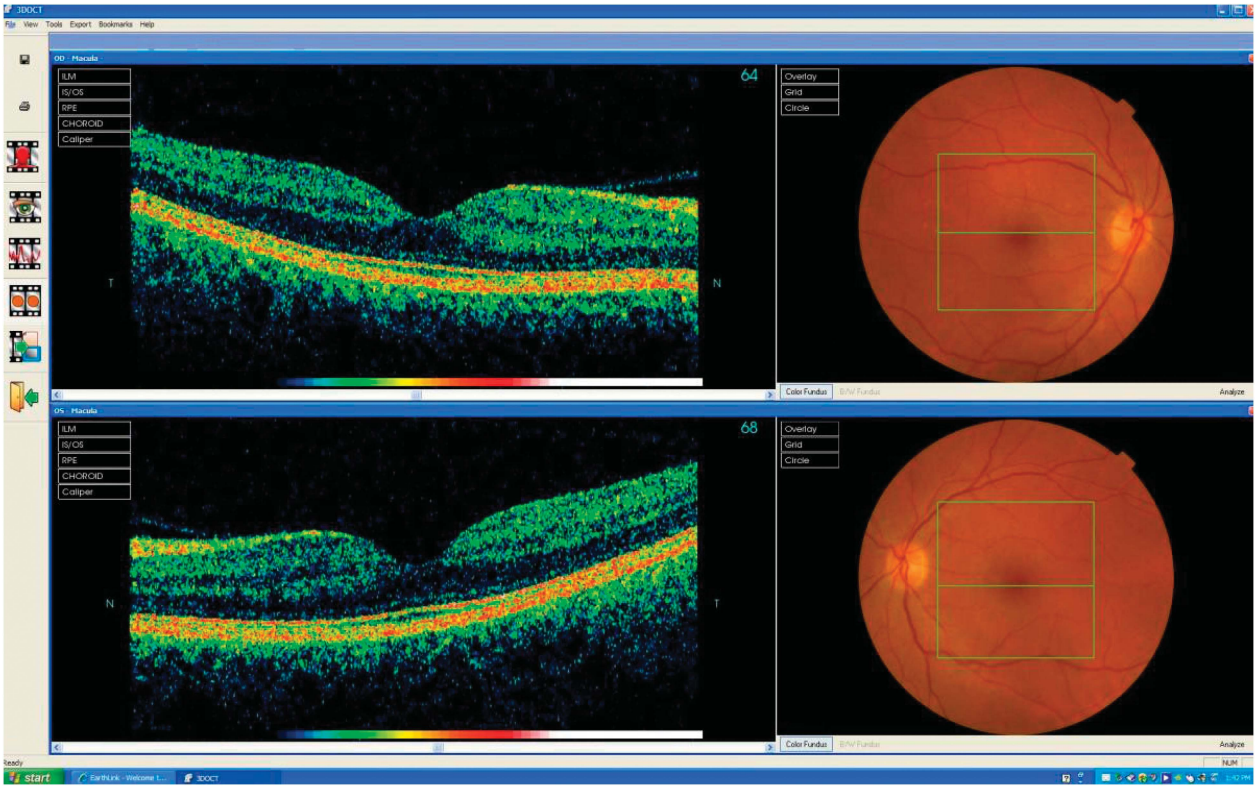

Figure 1 Fundus photograph (right side of image) and Topcon optical coherence tomographic image showing cross-section of the retina (left side of image) of a patient in the A/DM group (right eye: top and left eye: bottom). This patient is a 72-year-old Caucasian female with type 1 DM and RA, with onset of both diabetes and arthritis at the same time, 35 years previously. Retinal (fundus) images are normal and show no sign of diabetic retinopathy.

years of disease who also had coexisting OA seen in this one retinal practice in West Virginia between January 1996 and August 2008. All patients had been followed from date of their initial examination until the closing date of the study (August 2008) or until date of their last visit. The last recorded chart visit was used as the evaluation point for each patient.

High-quality digital fundus photography images (using the Ophthalmic Imaging System, Winstation, Sacramento, CA, USA) with a Topcon Fundus Camera (Topcon Medical Systems, Inc., Oakland, NJ, USA) from each patient were evaluated in a masked and random manner by an experienced retinal specialist, who was a stranger to the patients reviewed the fundus photographs and graded them for retinopathy using the Early Treatment of Diabetic Retinopathy Scale[12] (an extension of the modified Airlie House Classification Method) and recorded the findings (Figure 1). Fundus photographs were graded as without retinopathy (normal), having nonproliferative disease (NPDR), or having proliferative retinopathy (PDR). The worst eye from each patient was selected for statistical analysis (Table 2). This procedure represents the gold standard for evaluation and grading of DR.[13] The use of this grading system is supported by several US national studies of DR in the general diabetic population.[2,3,12]

The diagnosis of hypertension was established by patient history with previous physician-based diagnosis and was supported by anti-hypertensive medications listed in the charted 'medication list'. Information about chronic use of aspirin was obtained through patient history if aspirin was used 'on a daily basis.' Review of patients' use of non-aspirin pain medications including the use of NSAID was documented. Comparison of use of these medications between the arthritic–diabetic patient group and the non-arthritic–diabetic patient group, and correlation of these non-aspirin pain medications with the occurrence of DR was studied.

Statistics

The Student's *t*-test (two sided) was used to compare means of continuous data. The Fisher's exact test (two-tailed) was employed for statistical analysis of dichotomous data. The study sample size was determine by inclusion of all patients in the study group meeting the criteria of 20 or more years of diabetes and coexisting arthritis.

Table 2 Diabetic retinopathy in patient with and without osteoarthritis

Type of diabetic retinopathy	Type of diabetes mellitus	Number of patients/type of diabetes Mellitus	Number and percent of patients with or without diabetes mellitus who developed osteoarthritis		Odds ratio	*P*-value[a]
$n=170$			Regardless on timing of onset of osteoarthritis A/DM ($n=85$)	NoA/DM ($n=85$)		
Proliferative (PDR) $n=91$	IDDM	55	9/55 (16.4%)	51/55 (92.7%)	0.016	<0.001
	NIDDM	30	3/30 (10.0%)	28/30 (93.3%)	0.009	<0.001
	IDDM & NIDDM	85	12/85 (12.9%)	79/85 (92.9%)	0.012	<0.001
Non-proliferative (NPDR) $n=18$	IDDM	55	9/55 (16.4%)	4/55 (7.3%)	2.474	0.237
	NIDDM	30	3/30 (10.0%)	2/30 (6.7%)	1.544	1
	IDDM & NIDDM	85	12/85 (12.9%)	6/85 (7.1%)	2.154	0.212
No diabetic retinopathy $n=61$	IDDM	55	37/55 (67.3%)	0/55 (0%)	Infinity	<0.001
	NIDDM	30	24/30 (80.0%)	0/30 (0%)	Infinity	<0.001
	IDDM & NIDDM	85	61/85 (71.8%)	0/85 (0%)	Infinity	<0.001

Abbreviations: NS, non-significant; A/DM, osteoarthritic patient group with long-term diabetes of 20 years or more duration; NoA/DM, long-term diabetic patient without co-existing clinical arthritis; IDDM, insulin dependent diabetes; NIDDM, non-insulin dependent diabetes.
[a] Fisher Exact test, two-tail.

When the expected cell frequency was small, the χ^2 test was used. The comparison of the entire A/DM and NoA/DM groups, as well as comparison of insulin-dependent and non-insulin-dependent diabetic patients within each group for occurrence of DR was preplanned before beginning the study. Evaluation of sequence of disease onset, hypertension, smoking, level of glycosolated hemoglobin, and use of pain medication including aspirin was planned before beginning the study (Table 1). Comparison of occurrence of PDR relative to the timing of sequence of the onset of the diabetes relative to the arthritic symptoms was evaluated (Table 3).

Results

Both the groups of patients, A/DM and NoA/DM, comprised mainly white adults, slightly more women than men in their mid-60s with no significant differences (Table 1). The groups showed also no significant differences in their level of hemoglobin A1c, the presence of hypertension, and chronic use of aspirin or history of smoking. Of the 85 patients with A/DM, a specific time of onset of the osteoarthritic symptoms could be determined in 80/85 (94.1%) patients.

PDR developed in 12/85 (12.9%) of the A/DM patients compared with 79/85 (92.9%) of NoA/DM patients (Table 2; $P<0.001$). The rate of PDR seen in the non-osteoarthritic clinic patient population was similar in the insulin-dependent patient group compared with the non-insulin-dependent diabetic patient group (51/55 (92.7%) vs 28/30 (93.3%). The rate of PDR seen in the osteoarthritic group was far less than the non-osteoarthritic group but was similar when comparing IDDM and NIDDM within the osteoarthritic group (9/55 (16.4%) vs 3/30 (10.0%). NPDR developed in 12/85 (12.9%) of the A/DM patients compared with 6/85 (7.1%) of NoA/DM patients (Table 2; $P=0.2$).

If arthritis began the same year or before the onset of the diabetes, there was an even more significant reduction in the occurrence of proliferative DR. None of the 47 patients in whom the onset of arthritic symptoms was the same year or before the onset of their diabetes developed PDR compared with 10/33 (30.3%) of patients in which diabetes preceded development of OA ($P<0.0001$). In five patients, the relative onset was not able to be determined. This was not the case for NPDR were no significant difference was found in the groups (Table 3).

The use of non-aspirin pain medications including NSAID and other pain medications did differ between the two groups. A/DM group had a higher use of NSAIDs (28/85 vs 9/85: 32.9% vs 10.6%). Of the 28 patients in the A/DM group using these NSAID, PDR developed in 6/28 (21.4%), compared with 6/57 (10.5%) in the remainder of the A/DM group ($P=0.3$; Table 4). No patients in this study were found to be using or to have used anti-metabolite arthritic treatment(s). In both the A/DM group and the NoA/DM group slightly more than roughly 60% of patients in each group were referred to the retina 1

Table 3 Diabetic retinopathy in patients with osteoarthritis relative to onset of diabetes

Type of diabetic retinopathy	Type of DM	Number of patients/type of DM	Osteoarthritis onset prior to or same year as DM $n=47$	Osteoarthritis onset after the year of onset of DM $n=33$	Odds ratios	*P*-value*
Proliferative diabetic retinopathy (PDR) $n=10$	IDDM	51	0/28 (0%)	7/23 (30.4%)	0	0.002
	NIDDM	29	0/19 (0%)	3/10 (30.0%)	0	0.032
	IDDM & NIDDM	80**	0/47 (0%)	10/33 (30.3%)	0	<0.0001
Non-proliferative diabetic retinopahty (NPDR) $n=11$	IDDM	51	6/28 (21.4%)	2/23 (8.7%)	2.808	0.269
	NIDDM	29	3/19 (15.8%)	0/10 (0%)	Infinity	0.532
	IDDM & NIDDM	80	9/47 (19.1%)	2/33 (8.7%)	3.619	0.113
No diabetic retinopathy $n=59$	IDDM	51	22/28 (78.57%)	14/23 (60.87%)	2.317	0.222
	NIDDM	29	16/19 (84.21%)	7/10 (70.0%)	2.216	0.221
	& NIDDM	80	38/47 (80.85%)	21/33 (63.63%)	2.385	0.121

Abbreviations: NS, non-significant; A/DM, osteoarthritic patient group with long-term diabetes of 20 years or more duration; NoA/DM, long-term diabetic patient without co-existing clinical arthritis; IDDM, insulin dependent diabetes; NIDDM, non-insulin dependent diabetes.
*Fisher exact test two-tail is used for the whole table.
**Patients with DM who had an onset of their osteoarthritis prior or the same year as DM had very significantly less proliferative PDR than patients with their osteoarthritis onset after the year of onset of their DM.

Table 4 Occurrence of PDR in patients with pain medication

Patient group	Type of DM	a: Number of PDR in patient without pain medicine*	b: Number of PDR in patients using Aspirin only**	c: Number of PDR in patients using NoAPM & NSAIs***	b + c: Number of patient using pain medicine (A + NoAPM + NSAIs)****
1. ‡ 12 patients with PDR in the 85 patients with A/DM	IDDM &NIDM	4/41 (9.6%)	2/16 (12.5%)	6/28 (21.4%)	8/44 (18.2%)
2.‡‡ 79 patients with PDR in the 85 patients with NoA/DM	IDDM &NIDM	47/49 (95.9%)	24/27 (88.9%)	8/9 (88.9%)	32/36 (88.9%)

Abbreviations: PDR, proliferative diabetic retinopathy; A/DM, osteoarthritic patient group with long-term diabetes of 20 years or more duration; NoA/DM, long-term diabetic patient without co-existing clinical arthritis; IDDM, insulin dependent diabetes; NIDDM, non-insulin dependent diabetes.
Pain medicine used: Aspirin, ‡NSAIs : non steroidal inflammatory anti infammatory drugs : A/DM – Valdecoxib (1), Propoxyphene & acetaminophen (4), Celecoxib (7), Naprosyn (4), Acetominophen (1), Ibuprofen (5), Pentzocine & Naloxone (1), Orphenadrine (1), Rofencoxib (1) and ‡‡NoAPM = no aspirin pain medicine – Propoxyphene and acetaminophen (1), Celecoxib (1), Acetominophen (1), Ibuprofen (1), Prednisone (1), Rofecoxib (1), Oxycodone and Acetominophen (1), Tramadol (1), Hydrocodone and Acetominophen (1), Diclofenac (1), Indomethacin (1), Piroxicam (1).
Fisher Exact, two tailed test used. All the differences between ‡ and ‡‡ are significant ($P<0.001$), None of the difference are significant between patients without pain medicine * compared with the ones with pain medicine **, or *** or ****.

specialist by their primary eye care specialist, either a general ophthalmologist or an optometrist.

Discussion

In 1964, Powell and Field[14] reported better than expected retinal appearance in 34 patients with longstanding diabetes and coexisting rheumatoid arthritis including one patient who had suffered from diabetes for 43 years and yet displayed no evidence of DR on fundus examination. Speculation about the source of the protection from retinopathy suggested inhibition of complement by salicylates, but *in vitro* studies of these patients and additional studies over the years have failed to confirm the use of salicylates as protective.[15,16]

In our patients, we confirmed the observation that arthritic diabetic patients might have a relative protection from DR, but here we identify not rheumatoid arthritis patients, but specifically osteoarthritic patients found significantly less development of proliferative retinopathy (neovascularization or angiogenesis) in these patients compared with non-arthritic control patients. We found this effect not to be dependent on aspirin use nor on other anti-pain and anti-inflammatory NSAIs drugs. PDR had a tendency to develop more frequently in the A/DM patients using Aspirin alone or NSAID.

Our data show that the A/DM group of patients had significantly fewer cases of PDR ($P<0.001$). Those patients who developed OA before or in the same year as they developed diabetes had significantly fewer cases of PDR than diabetic patients who developed OA after they developed mellitus ($P<0.001$). This was seen in both insulin-dependent and non-insulin-dependent diabetic patients (Table 3).

One hypothesis is that the internal landscape created by osteoarthritic and arthritic changes may release pro-inflammatory proteins into the blood and these protein(s) may create a protective environment in distant organs in the body, for example, the eye. Normal joint cartilage contains no blood vessels, and high concentrations have been identified within the cartilage of anti-angiogenic factors such as chondromoldulin-1 (chM-1) and thrombospondin-1 (TSP01).[17] Articular cartilage provides a unique environment in which blood vessel growth is regulated by endogenous angiogenesis inhibitors and matrix constituents, as well as by growth factors produced by chrondrocytes, subcondrial bone, and synovium.[18] One or more of these products may have a role as a 'protective factor' in osteoarthritic diabetic patients.

In general, tissue angiogenesis results from an imbalance between pro- and anti-angiogentic factors. For example, one joint product of inflammation, thrombospondin, a cytokine, has both CD36 and CD47 receptors,[19] which are capable of eliciting opposite effects on the retinal pigment epithelial cells and may in some way be sensitive to the optimal level of inflammation needed for vascular protection. If this 'cellular cytokinetic rheostat' effect exists, then a therapeutic window may exist. This 'window' may be a condition in which just enough (sufficient) inflammation may be present to create a favorable intravascular environment to reduce the deleterious effects of hyperglycemia on leukostasis, platelet aggregation, and perhaps even neovascularization in distant organs. The amount of inflammation appears to be needed to be protective can be imagined like that seen in a U-shaped curve. Both too little and too great an amount of inflammation is not protective, but just within the therapeutic 'window', the products of joint inflammation may in effect 'coat' the inside of the vessels in distant organs protecting them from that step of leukocyte adhesion which may be the early trigger in neovasuclar formation of abnormal vessels. We know from tumor studies and ACAID[20] that a delicate, different, immune environment exists in the eye, and particularly in the retina as the evolution of the understanding of the role of VEGF on subretinal neovascular proliferation continues.[21]

It may be possible that the titer of environmental factors that control angiogenesis is interpreted within individual endothelial cell as a balance between pro-apoptotic and survival signals is altered. TSP-1 may triggers a signaling pathway of its own that renders endothelial cells generally insensitive to all incoming stimulatory signals.[20] Another hypothesis is that arthritic joint inflammation in diabetic patients may provoke development of a protective milieu against PDR. One possibility is that pro-inflammatory cytokines from inflamed joints may protect retinal vasculature. Loss of articular cartilage because of extracellular matrix breakdown is the hallmark of arthritis, and elevated levels of serum thrombospondin and ADAMTS-12 (a disintegrin and metalloprotease with thrombospondin motifs) has been shown to be elevated in both OA and rheumatoid arthritis.[22] Thrombospondin and chondromoldulin-1, both angiogenesis inhibitors known to come from inflamed articular tissue have been shown to have a key role in creating and maintaining the immune privilege in the eye and in blocking neovascularization.[23]

In this study, various possible confounding factors were evaluated, including hyperglycemic control, chronic use of aspirin, hypertension, and smoking, and did not appear to have a role. NSAID use within the A/DM group was not associated with increased occurrence of PDR ($P=0.3$) but did not reach statistical significance. A recent editorial speculated that lipooxygenase inhibition in OA has a potential symptomatic and disease-modifying effect.[24]

Clinical practice and research efforts related to OA have been hampered by an inadequate case definition. Much of the difficulty is due to a lack of agreement between X-rays evidence of OA and a patient's report of pain at that site. Such discordance between reported pain and radiographic evidence of OA has been attributed to several factors. In diabetic patients, it is possible that diabetic neuropathy, although first causing some pain, may gradually inhibit the ability to feel pain that might have otherwise been reported by those patients without neuropathy.[25] Therefore, some of the patients classified in the group 'no clinical OA' NoA/DM probably had some radiological changes of OA. Moreover, some of these patients without clinical OA might also been the patients with the most severe diabetes with neuropathy and PDR. This might have a role in the higher incidence of PDR in this group. However, PDR was not observed significantly more frequently in patient taking more pain medicine.

In conclusion, in the general diabetic population roughly half of the patients have some form of arthritis. In this study, we observed that in long-term DM, PDR was significantly associated with the absence of concomitant clinical OA ($P<001$). This observation was highly significant if the onset of the arthritis was the same year or prior to the onset of the diabetes ($P<0.001$).

Summary

What was known before

- Over the last 20 years, we had noticed a remarkable trend whereby patients with coexisting long-term diabetes and long-term arthritis failed to develop diabetic retinopathy at the expected rate of individuals with diabetes but without arthritis. A study of occurrence of diabetic retinopathy among diabetic patients in one rural practice in West Virginia was undertaken in which two groups were studied, one with long-term arthritis and one without long-term arthritis. The diabetic patients with arthritis appeared to demonstrate far less retinopathy than would have been expected. Various related factors were studied to try further catagorize the characteristics of this observation.

What this study adds

- This study adds to the literature a new perspective of the influence (in this case the beneficial influence) of one disease (arthritis) on another (diabetes). These 'overlap' groups, sharing both diseases, appear to develop diabetic retinopathy less severely and this may be an important observation leading to exploration of the 'protection' that arthritis provides here, whether by some vascular-protective immune molocule or by other means. This paper is important because it may open an interesting avenue of research if components of the possible 'protection' can be identified and used to help all diabetic patients.

Conflict of interest

The authors declare no conflict of interest.

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